REMARKS

Claims 1, 4-8, and 100-104 are currently under examination in the application. Claims 2, 9, 10, 12-13, 21-22, 24-48, 59 and 65-93 have been withdrawn from consideration due to the Examiner's previous restriction requirement. Claims 3, 11, 14-20, 23, 49-58, 60-64, 94-99, and 105-106 have been canceled. Claim 1 is presently amended, and claims 107 and 108 are new. Support for the amended and new claims is found in the present application, e.g., at page 2, lines 8-14, page 3, lines 23-28, page 16, lines 1-6. Claims 100-102 and 104 have also been amended, but only to change the dependency of each to claim 1. (See Part II.B)

These claims have been amended, withdrawn or canceled without prejudice to, or disclaimer of, the subject matter thereof. Applicants reserve the right to file divisional and continuing applications directed to the subject matter of any claim withdrawn or cancelled for any reason. By these remarks and amendments, Applicants do not acquiesce to the propriety of any of the Examiner's prior rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

I. Claim Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1 and 4-8 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. According to the Examiner, "[t]here is no support in the specification for the limitation 'during rehabilitation of said animal from stroke and after the acute stroke phase of said stroke in said animal has ended,' as recited in claim 1."

Without acquiescing to the propriety of this rejection, Applicants have amended claim 1 to remove the limitation "after the acute stroke phase of said stroke in said animal had ended." Applicants further note that the limitation "during rehabilitation of said animal from stroke" finds specific support in the instant specification. For example, Page 3, lines 23-25 of the Specification teaches that "[c]ognitive training protocols are employed in rehabilitating stroke patients (stroke rehabilitation), particularly rehabilitating impaired or lost sensory-motor function(s)."

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 1 in this section under § 112, first paragraph.

II. Claim Rejections under 35 U.S.C. § 112, second paragraph

A. Claims 1, 4-8

The Examiner has rejected claims 1 and 4-8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point put and distinctly claim the subject matter which applicant regards as the invention. According to the Examiner "claim 1 recites the broad recitation 'administering to said animal before, during, and after said providing step', and the claim also recites 'wherein said administering occurs during rehabilitation of said animal from stroke and after the acute phase of said stroke' which is the narrower statement of the range limitation."

Applicants assert that this rejection is moot in view of the claim amendments, which specify that the providing and administering steps occur during rehabilitation and in conjunction with each other. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under § 112, second paragraph.

B. Claims 100-104

The Examiner has rejected claims 100-104 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point put and distinctly claim the subject matter which applicant regards as the invention. The Examiner notes that "[c]laims 100-104 depend on claim 98, which has been cancelled" and that "[t]herefore, the metes and bounds of patent protection sought for this specific limitation had not been defined."

In response, Applicants have amended the claims so that they all depend directly or indirectly from pending claim 1. Accordingly, Applicants request that the Examiner reconsider and withdraw this rejection under § 112, second paragraph.

III. Claim Rejections under 35 U.S.C. § 103

The Examiner has sustained the rejection of claims 1 and 4-8 under 35 U.S.C. § 103 as obvious over United States Patent Number 5,547,979 ("Christensen") in view of the Merck Manual ("Merck"). As set forth below, Applicants traverse for the following reasons and in view of the current amendments.

To maintain a proper rejection under 35 U.S.C. § 103, the Examiner must meet four conditions to establish a *prima facie* case of obviousness. First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the

Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations, either expressly or inherently.[1] Fourth, if an obviousness rejection is based on some combination of prior art references, the Examiner must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test").[2] Following the Supreme Court's decision in *KSR v. Teleflex*,[3] this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the Court's flexible approach of *Graham v. Deere*.[4]

Establishing the obviousness of a patent claim based upon a combination of prior art requires a showing of a reason to combine that prior art and that each and every element of the invention is taught or suggested. This requirement captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art."[5] It is therefore "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does."[6] A "flexible" "teaching, science or motivation" ("TSM") "test remains the primary guarantor against a non-statutory hindsight analysis" in obviousness cases.[7]

With this framework in place, the Applicants now will specifically reply to the four sets of arguments provided by the Examiner in the Office Action. In each case, the Examiner's summary of Applicants' arguments is also provided.

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[1] *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995); *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001)

[2] *In re Dembiczak*, 175 F.3d 994, 998 (Fed. Cir. 1999).

[3] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

[4] *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). 127 S. Ct. 1727 (2007).

[5] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

[6] *Takeda Chem. v. Alphapharm*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *KSR v. Teleflex*) (emphasis added).

[7] *Ortho-McNeil Pharma. v.Mylan Labs.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

A. Set One

1. Examiner's Summary

"Applicant argues that Christensen relates to administration of rolipram during the initial acute phase of a stroke episode to treat acute tissue injury. Christensen does not teach the administration of the compounds after the acute phase of the inflammatory event has ended or during training. Christensen along with the Merck Manual does not teach that one could achieve performance gain during the training by the administration of phosphodiesterase inhibitors before or during training. Specifically, Applicants go into great detail regarding the mechanism of action of PDE4 inhibitors, including inhibiting the inflammatory response often associated during the immediate time period following a brain injury. Therefore, Christensen effectively teaches away from the repeated application of PDE4 inhibitors in conjunction with stroke, due to the early production of TNF during the initial stages of an inflammatory event"

Office Action at p. 8

2. Examiner's Response

"This is not persuasive for several reasons. At the outset, the amended claims still recite administration of PDE4 inhibitors before, during, or after cognitive training, which means administration at any time during the treatment period." "The claim then goes on to recite that the PDE4 inhibitor is administering [sic] during the rehabilitation phase of a stroke patient, which present several 112 issues as stated above." "At any rate, the cited prior art still reads on the instant claims because Christensen does not limit the administration of PDE4 inhibitors to any particular time period or treatment window of a stroke patient. In fact, Christensen clearly recites the treatment of a stroke patient, which also includes the time after the acute phase of stroke episode or the rehabilitation period involving cognitive training." "Further, it is not clear when exactly does inflammation subside during the treatment period of a stroke patient, since low levels of inflammation could last well into the rehabilitation periods. Applicant is reminded that the standard for obviousness is not absolute but a reasonable expectation of success."

Office Action at pp. 8-9.

3. Applicant's Reply

As amended, the claims specify that the administration of a PDE4 inhibitor must occur during stroke rehabilitation. Hence, administration of the PDE4 inhibitor is "not at any time during the treatment period."

The Examiner provide no evidentiary basis for the assertion that Christensen covers PDE4 inhibitor administration during all stages of stroke treatment

The claim amendments make explicit that the inhibitor is administered in conjunction with said cognitive training during rehabilitation so that the inhibitor will enhance CREB pathway function during cognitive training.

These recitations also underscore the deficiency in Examiner's position that Christensen teaches administering a PDE4 inhibitor during the rehabilitation period involving cognitive training. In fact, Christensen does not mention or suggest the term "rehabilitation" at all. And the word "stroke" occurs only twice in *Christensen*. The first time is in the Specification:

> TNF also has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, **stroke** and circulatory shock.

Christensen, Col. 5, lines 20-25

The second time is in claim 1:

> **1.** A method of treating tissue injury, reperfusion injury, myocardial infarction, **stroke** or circulatory shock in a mammal, which comprises administering to said animal in need thereof an effective TNF inhibiting amount of a compound according to the formula . . ..

Christensen, Col. 12, lines 27-54

These two occurrences of the term "stroke" and their specific link to TNF accord with the entire *Christensen* patent, which is entitled "TNF Inhibition" and is directed to inhibiting TNF activity in TNF-mediated diseases or disease states. In addition, Applicants submitted a wealth of evidence in their previous reply showing an early pro-inflammatory role for TNF in stroke pathology, defining a narrow therapeutic window immediately after stroke onset.

Despite this converging evidence, the Examiner continues to assert that "Christensen does not limit the administration of PDE4 inhibitors to any particular time period or treatment window of a stroke patient" and that "[i]n fact, Christensen clearly recites the treatment of a stroke patient, which also includes the time after the acute

phase of stroke episode or the rehabilitation period involving cognitive training." Applicants do not understand the basis for such a sweeping assertion.

Christensen does not expressly or inherently disclose administering a PDE4 inhibitor during rehabilitation of a stroke patient.

Christensen does discusses administering a PDE4 inhibitor during stroke rehabilitation. It does not mention rehabilitation, and to the extent it discloses therapeutic compounds, their efficacy is limited to TNF-inhibitory actions in acute stroke pathology, particularly as anti-inflammatory agents. Without relying on knowledge found only in the Applicant's specification, there is no basis for the assertion that Christensen discloses administering such compounds during rehabilitation – only unfounded speculation.

Nor does Christensen disclose this limitation inherently. The Examiner asserts, for example, that "it is not clear when exactly does inflammation subside during the treatment period of a stroke patient, since low levels of inflammation *could* last well into the rehabilitation period." Applicants note that a mere possibility is not inevitability, and for this reason, fails to meet the requirements for inherency. An inherent characteristic must be the "'natural result' flowing from" the teachings or disclosure of the prior art, [8] and the characteristic must necessarily be present – not be just a possibility or even a probability.[9] Invoking a particular set of circumstances that might lead to administering the TNF inhibitor during the rehabilitation period, as the Examiner has done here, is not sufficient.[10]

The Examiner concludes with the statement that "that the standard for obviousness is not absolute but a reasonable expectation of success." But this standard is inapplicable. A reasonable expectation of success applies to the ultimate determination of obviousness – not to what Christensen teaches in the first place. But Christensen does not disclose the claimed administering step explicitly, nor does it meet the threshold requirements to make this showing inherently.

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[8] *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001).

[9] *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient. . . the disclosure [must be] sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function")

[10] *See In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency").

B. Set Two

1. Examiner's Summary

"Applicant argues that there is no reasonable expectation of success by combining the teachings of Christensen with cognitive training during rehabilitation. Applicant also argues that the Merck Manual can only be read to teach cognitive training after the acute phase of a stroke."

Office Action at p. 9.

2. Examiner's Response

"This is not persuasive because as stated above, Christensen teaches, in general, the treatment of a stroke patient by administering a PDE4 inhibitor, which encompasses the entire treatment regimen including rehabilitation. Furthermore, the Merck Manual clearly states that a training protocol should be started as early as possible towards a patient's rehabilitation towards to stroke. Such rehabilitation includes encouragement, orientation to ones environment, eating, dressing, toilet functions, other basic needs, passive exercise, particularly of paralyzed limbs, and breathing exercises, if possible, should be started early. The time period may encompass when the patient is still in or just recovering from the acute phase of the stroke episode. Nonetheless, it is clear that the Merck Manual teaches cognitive training after the acute phase of a stroke. It is Examiner's position that it would be obvious to administer PDE4 inhibitors as taught by Christensen in combination with rehabilitation after the acute phase of stroke. Therefore, since both references teach treating stroke patients, it is obvious to combine these treatment regimens because both are drawn to the same purpose as well as for the combined therapeutic effect. For these reasons, Examiner submits that there would be a reasonable expectation of success in treating stroke patients as instantly claimed."

Office Action at pp. 9-10 (emphasis added).

3. Applicant's Reply

With respect to Examiner's assertion that "Christensen teaches, in general, the treatment of a stroke patient by administering a PDE4 inhibitor, which encompasses the entire treatment regimen including rehabilitation," Applicants reiterate that this position is not supported by the evidence. Christensen does not mention rehabilitation and mentions stroke only twice, both times in connection with TNF-mediated disease states and their treatment by TNF-inhibitors.

The Examiner continues to misinterpret and misapply Merck

Applicants further assert that the Examiner is not properly interpreting the Merck Manual. In their previous reply, the Applicants carefully parsed out the teachings in Merck, showing that "Treatment" consists of two phases: "Immediate care" and "Rehabilitation and aftercare." Immediate Care does not encompass cognitive training procedures – only passive procedures: "Passive exercise, particularly of paralyzed limbs, and breathing exercises, if possible, should be started early."[11] Conversely, only the Rehabilitation phase includes **active** procedures that bear on cognitive training, including procedures accompanying "occupational and physical therapy." *Id. Merck Manual* at 1456.

Despite these observations, the Examiner continues to misrepresent the teachings in Merck. For example, the Examiner suggests above – and directly asserts elsewhere in the Office Action[12] – that cognitive training protocols include the passive procedures listed under Immediate care. Because this assertion is misplaced, it does not prove a proper basis to argue that Merck somehow teaches that cognitive training and rehabilitation occur immediately after stroke. This view is also scientifically inconsistent with other evidence previously submitted to the Examiner, including the *Guideline*.

The Examiner improperly invokes one of skill in the art to cover crucial claim limitations that not disclosed in Christensen or Merck or their combination.

Replying on the knowledge of one skilled in the art, the Examiner asserts that "since both references teach treating stroke patients, it is obvious to combine these treatment regimens because both are drawn to the same purpose as well as for the combined therapeutic effect." This argument is wrong and misleading for several reasons.

At the outset, the skilled artisan invoked by the Examiner does not merely combine Christensen and Merck. The Examined has also endowed the skilled artisan with knowledge of a crucial claim limitation found only in the Applicant's disclosure: administering a TNF inhibitor in conjunction with cognitive training, so that CREB

[11] Merck Manual at 1455.

[12] Office Action at pp. 6-7

pathway function will be enhanced during cognitive training. In other words, because this limitation is not disclosed by Christensen, Merck or their combined teachings, the Examiner improperly resorts to one skilled in the art to cover this gap.

Such resort to one skilled in the art is highly suspect because it strongly suggests improper hindsight reconstruction. *See W.L. Gore & Assocs., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 1553 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."); *Ryko Mfg. Co. v. Nu-Star, Inc.,* 950 F.2d 714, 718 (Fed. Cir.1991) (Skill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process.). Examining the asserted justification for combining the references reveals the fallacy in the Examiner's position.

First, even if Christensen and Merck both relate to stroke treatment, they are **not** drawn to the same purpose. The purpose of administering a TNF inhibitor during stroke is to treat disease states resulting from unregulated TNF-action. In particular, such inhibitors may be useful in inhibiting the early action of TNF in inflammatory responses. In contrast, cognitive training is directed to improving cognitive functions, such as sensory-motor skills, during rehabilitation of stroke patient. Such temporally and mechanistically distinct purposes do not support the Examiner's unfounded assertion that that one skilled in the art would combine them simultaneously.

Also unavailing is the Examiner's second argument: that one would simultaneously administer the two regimens because of the combined therapeutic benefit. This assertion presents a somewhat preposterous scenario: a skilled artisan, faced with a stroke patient suffering from brain inflammation, would somehow deem it wise to treat the brain injury in conjunction with a cognitive training protocol directed to the neurologically compromised patient. Under the Examiner's contrived scheme, the onset of a TNF-mediated disease – which can be the only trigger for administering a drug – would logically lead the skilled artisan to apply cognitive training as well. Such a rationale is backwards and strained, and it can only be explained by improper hindsight reconstruction. Without knowledge gleaned only from the Applicant's

specification and claims, there is no reasonable basis for believing that there would be a combined therapeutic effect.

In short, just because two treatment regimens are directed to stroke, this does NOT automatically mean that one skilled in the art would combine them. To the contrary, the art emphasizes the need for caution and restraint when considering rehabilitation. For example, Merck shows that that during "rehabilitation and aftercare "early, repeated appraisals of the patient's status by physician, physiotherapist, and nursing staff promote design of a remedial program. Merck also underscores the complexity and vigilance when contemplating different drug treatment regiments for stroke:

> Heparin may stabilize symptoms in evolving stroke, but anticoagulants are useless (and possibly dangerous) in acute completed stroke, and are *contraindicated* in hypertensives because the increased possibility of hemorrhage into the brain or other organs. Although the timing is controversial, anticoagulants may be started to prevent recurrent cardiogenic emboli. Clot lysing agents, including tissue-plasminogen activator and streptokinase, are being evaluated for the very early treatment of stroke.

Merck at 1455.

In sum, even if the Christensen and Merck references can be combined, it is wholly improper to impose the additional limitation – as the Examiner has – to simultaneously administer the two different treatments, whose roles in stroke are mechanistically, temporally, and clinically distinct. Guided by knowledge only in the Applicant's disclosure, the Examiner has stretched the rationale for combining to encompass the crucial missing limitations. And to do so, the Examiner has created and customized one of skill in the art to meet all deficiencies. Absent direct evidence, the Examiner has not established a prima facie case, and hence the rejection should be withdrawn.

B. Set Three

1. Examiner's Summary

> "Applicant argues hindsight reconstruction in the argument that performance gain would necessarily result if rolipram therapy is administered immediately following stroke and cognitive therapy is begun as early as possible after stroke. Applicant argues that the Examiner has provided no evidence that the administration timeline contemplated by Christensen overlaps with that described by the Merck Manual. Specifically, Applicant argues that neither

> of the cited references teach or suggest 'long lasting performance gain effected by enhancement of CREB pathway function during rehabilitation.'"

Office Action at 10.

2. Examiner's Response

> "This is not persuasive because said performance gain of a cognitive task in a stroke patient is an inherent property when the same compound is administered to the same patient at the same dose. Therefore the "long lasting" and 'enhancement of CREB pathway function limitations are met because they are inherent properties." Moreover, the Examiner interprets performance gain of a cognitive task as covering a wide range of impairments, which include aphasia (language/speech disturbance) and apraxia (impaired ability to carry out motor activities), as disclosed in Applicant's own disclosure. Essentially, the scope of the instant claims covers administration of the phosphodiesterase inhibitors at any time to the patient. Therefore, Applicant's assertion that Christensen is simply teaching the administration of rolipram during the acute phase of the stroke to reduce TND still meets the limitation of the instant claims as it relates to the Merck Manual reference. Nonetheless, Applicant is invited to show factual data that performance gain would not result in the method taught by the cited prior art references."

Office Action at pp. 10-11.

3. Applicant's Reply

The flaw in the Examiner's argument, as revealed in the preceding discussion, is that it rests on a false assumption: that one skilled in the art would necessarily administer a TNF inhibitor, as disclosed in Christensen, in conjunction with cognitive training, as disclosed in Merck. The cited references do not teach or suggest this limitation, alone or in combination, expressly or inherently. And the Examiner's invocation of one skilled in the art having knowledge of the Applicant's disclosure to cover this gap is not proper or justifiable as explained in detail above.

The assertion that performance gain of a cognitive task in a stroke patient is an inherent property when the same compound is administered to the same patient at the same dose is therefore a red herring. Absent this temporal link, a compound administered to treat a TNF-mediated disorder will NOT necessarily be at the same dose – and may well not even be present – when that same patient is later treated with a cognitive training protocol.

D. Set Four

1. Examiner's Summary

"[T]he examiner's conclusion of obviousness is based on improper hindsight reasoning"

Office Action at p. 11.

2. Examiner's Response

"[I]t must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper."

Office Action at p. 11.

3. Applicant's Reply

As discussed above, the Examiner has relied on knowledge gleaned only from the applicant's disclosure: that a PDE4 inhibitor is also able to enhance cognitive performance **when** it is administered in close conjunction with cognitive training, such that the drug activates CREB pathway function during cognitive training. This link is not taught or suggested in the prior art inherently or explicitly. And the Examiner's reliance on one skilled in the art to fill this gap is simply wrong. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account

Respectfully submitted,

/djpelto Reg. No. 33754/

Date: January 28, 2010

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